Journal of Surgical Oncology 63:107–111 (1996)

Oral Adjuvant Chemotherapy with Carmofur (HCFU) for Colorectal Cancer: Five-Year Follow-up. Tokai HCFU Study Group—Third Study on Colorectal Cancer

KATSUKI ITO, MD, AKIHIRO YAMAGUCHI, MD, KAORU MIURA, MD, TOMOYUKI KATO, MD, SHOZO BABA, MD, SUMIO MATSUMOTO, MD, MASATAKA ISHII, MD, AND HIROSHI TAKAGI, MD

From the Second Department of Surgery, School of Medicine, Nagoya University, Nagoya (K.I., H.T.); Department of Surgery, Ogaki Municipal Hospital, Ogaki-shi, Gifu-ken (A.Y.); Department of Surgery, Fujita Health University, Toyoake-shi, Aichi-ken (K.M.); Department of Gastroenterological Surgery, Aichi Cancer-Center Hospital, Nagoya (T.K.); Second Department of Surgery, Hamamatsu University, Hamamatsu-shi, Shizuoka-ken (S.B.); Department of Surgery, Second Teaching Hospital, Fujita Health University, Nagoya (S.M.); Department of Surgery, Okazaki Municipal Hospital, Okazaki-shi, Aichi-ken, (M.I.), Japan

Background: A joint study was performed by the Tokai HCFU study group, which included seven institutions, to examine the value of oral administration of Carmofur (HCFU), a 5-fluorouracil (5-FU) derivative, for postoperative adjuvant chemotherapy in patients with colorectal cancer undergoing curative resection.

Methods: The patients were divided into two groups, a control group receiving no HCFU and a group administered HCFU for 1 year, using a centralized registration system by telephone. Among 173 patients entered into this study, 159 evaluable cases were analyzed for evaluation of the drug.

Results: The cumulative 5-year disease-free rate of patients who received HCFU was significantly increased compared with the control group. In particular, the rate was much higher in patients with colon cancer. No severe side effects arose from adjuvant chemotherapy with HCFU.

Conclusion: Adjuvant chemotherapy with oral HCFU appears to provide a useful and safe postoperative treatment.

KEY WORDS: **adjuvant chemotherapy, colorectal cancer, Carmofur**

INTRODUCTION

Recently, adjuvant chemotherapy has been considered to provide an increase in the rate of survival after curative resection for colorectal cancer. Many studies on adjuvant chemotherapy, however, have used mainly intravenous infusion. 1-Hexylcarbamoyl-5-fluorouracil (Carmofur, HCFU, Mifurol) is a 5-FU derivative, oral anticancer drug developed by Hoshi et al. [1] and by Koyama [2]. The use of an oral anticancer drug for adjuvant chemotherapy is of great interest to oncologists because of its ease of administration. We previously reported the results of a randomized trial which showed the usefulness of the long-term oral administration of HCFU [3] in combination with mitomycin-C (MMC) as an adjuvant chemotherapy regimen, but the effectiveness of the oral administration of HCFU alone was not so clear. To clarify the efficacy of HCFU, a randomized, controlled study was performed by the seven institutions of the "Tokai Study Group on Adjuvant Chemotherapy with HCFU" in the Tokai district. As in previous reports [3,4], we describe the 5-year survival rate, disease-free survival rate, as well

Accepted for publication June 26, 1996.

Address reprint requests to Katsuki Ito, M.D., Second Department of Surgery, School of Medicine, Nagoya University, 65 Tsurumaicho, Showaku, Nagoya, Japan 466.

as the type of recurrence in patients with colorectal cancer followed for 5 years, along with the cumulative 5-year postoperative survival rate and disease-free survival rate.

METHODS

Patients who underwent a colorectal operation at one of seven clinical centers in the Tokai district during a 3-year period (from October 1, 1987 to September 30, 1990) were enrolled in the study. Patient eligibility was assessed as follows: a diagnosis of colorectal cancer, age less then 75 years, no severe complications such as severe heart disease or liver cirrhosis, macroscopically curative resection at operation, and no history of any other cancer either past or present. The eligible patients were assigned randomly by computer to one of two treatment groups using a centralized registration system by telephone.

Drug dosages were as follows: (1) arm A (control group), curative surgery alone; and arm B (HCFU group), starting 4 weeks after curative surgery, 8 mg/kg/day of body weight Carmofur (HCFU) was administered orally, divided two or three times per day, for 12 months. The collected case reports were examined by an evaluation committee at the Second Department of Surgery, Nagoya University.

The analytical method was based on "survival rates, disease-free rates, computing rules of the Japan Society for Cancer Therapy." Survival rates and disease-free rates were computed and analyzed using SAS life test procedures. The uniformity of the background factors were examined using the χ^2-test and U-test. Survival and disease-free survival rates were estimated by the Kaplan–Meier method and analyzed by the generalized Wilcoxon test and the log-rank test. In addition, patients who died from other diseases or unknown causes after the recurrence of colorectal cancer was identified were treated as "deaths from colorectal cancer."

RESULTS

A total of 173 patients at seven institutions were enrolled in the study (arm A, 85; arm B, 88). Of the 173 patients, the data for two were unsuitable for efficacy analysis (i.e., noncurative operation), the data for 12 (7%) patients (arm A, 2; arm B, 10) were considered "incomplete" due to protocol violation (i.e., other anticancer drugs were used in six cases, HCFU was not administered or incompletely administered in six cases). Thus, 159 (92%) of enrolled patients were considered evaluable and were the study subjects used for analysis (arm A, 82; colon cancer, 43; rectal cancer, 39; arm B, 77; colon cancer, 44; rectal cancer, 33) (Table I)

There were no statistically significant differences between the two arms in terms of background factors related to patient survival rate (Tables II, III). These background factors include age and sex as host factors (Table II); tumor size, location of tumor, macroscopical and histopathological depth of tumor (Borrmann's classification), lymph node metastasis and stage, classification of gross appearance of the tumor, histological type of tumor, lymphatic spread, and vascular invasion as the carcinoma factors (Table III).

TABLE I. Selection of Cases for Survival Study of Colorectal Cancer

	Arm A	Arm B	Total incidence n	Total incidence %
Entered cases	85	88	173	
Excluded cases	1	1	2	1
Eligible cases	84	87	171	99
Withdrawn cases	2	10	12	7
Evaluable cases	82	77	159	92

Evaluable patients in arm B received 146.0 g of HCFU (standard dosage) (Table IV). No difference in overall survival rates were seen among the 173 entered cases, but the disease-free survival rate was significantly higher for the HCFU-treated group (arm A, 63%; arm B, 77%) (log- rank test: $P = 0.0407$, g-Wilcoxon test: $P = 0.0348$) (Fig. 1). For the 159 completely eligible patients, the disease-free survival rate was also significantly greater for the treated group (arm A, 63%; arm B, 77%) (log-rank test: $P = 0.0469$, g-Wilcoxon test: $P = 0.0401$) (Fig. 2). For the various background factors, the increase in disease-free survival rates for the HCFU- treated group with colon cancer was found to be statistically significant (arm A, 69%; arm B, 86%) (log-rank test: $P = 0.0498$, g-Wilcoxon test: $P = 0.0436$) (Fig. 3). As for other factors, with regard to lymph node invasions a tendency of a difference was found (arm A, 49%; arm B, 70%) (log-rank test: $P = 0.0710$, g-Wilcoxon test: $P = 0.0533$) (Fig. 4)

Side effects due to HCFU appeared in 18 patients (20%) in arm B (Table V). These included pollakisuria (8 cases); a hot sensation (3 cases); dizziness (3 cases); numbness (2 cases); diarrhea (2 cases); and anorexia, micturition disorder, tinnitus, stomatitis, irritability, and nausea or vomiting in one case each. There were no severe side effects requiring the patient to be hospitalized or treatment more than simple discontinuation of drug; no hand-foot syndrome; and no alopecia.

DISCUSSION

Many controlled studies of postoperative adjuvant chemotherapy have been conducted, mainly in the United States. The outcomes in these studies, however, have not always been satisfactory [5–7]. In 1990, Moertel et al. [8] showed the efficacy of therapy with levamisole plus 5-FU, which is now the standard adjuvant chemotherapy in the United States for stage III colon cancer. The efficacy of this postoperative adjuvant chemotherapy has been

TABLE II. Comparison of Clinical Background Factors Between Arm A and Arm B Patients With Colorectal Cancer

		χ^2 test	U-test
Host factor			
Age		—	NS ($P = 0.163$)
Sex		NS ($P = 0.691$)	—
Tumor factor			
Tumor location		NS ($P = 0.515$)	—
Borrmann's classification		NS ($P = 0.892$)	—
Lymph node metast.	N[1]	—	NS ($P = 0.782$)
	n	—	NS ($P = 0.305$)
Serosal involvement	S	—	NS ($P = 0.585$)
	s	—	NS ($P = 0.648$
Lymphoduct spread	ly	—	NS ($P = 0.724$)
Vascular spread	v	—	NS ($P = 0.349$)
Clinical stage macro stage		—	NS ($P = 0.346$)
micro stage		—	NS ($P = 0.313$)
Type of histology		NS ($P = 0.913$)	—

NS, not significant.

TABLE III. Clinical Background Factors and Follow-up Data for Patients With Colorectal Cancer (n < 173)

	A	B		A	B
Tumor location: Colon	45	51	Lymphatic spread: ly0	14	19
Rectum	40	37	ly(+)	71	69
			Vascular spread: v0	45	47
Lymph node metast: macro			v(+)	40	41
N (−)	28	24			
N (+)	57	64	Type of histology		
Lymph node metast: micro			Well-differentiated adenocarcinoma	26	28
n (−)	54	49	Moderately differentiated adenocarcinoma	54	54
n (+)	30	39	Poorly differentiated adenocarcinoma	2	1
Not available	1	0	Mucinous carcinoma	2	4
Serosal involvement: macro			Not available	1	1
Mucosa	0	0			
Submucosa	0	0	Follow-up data		
Muscularis propria	13	8	Alive	64	64
Subserosa	27	27	Lost to follow-up	1	4
Serosa	37	44	Death from cancer	18	15
Invasion adjacent structures	8	9	Death from other causes	1	5
Serosal involvement: micro			Not available	1	0
Mucosa	0	1	Recurrence	31	19
Submucosa	1	3	No recurrence	47	66
Muscularis propria	15	10	Not available	7	3
Subserosa	48	54			
Serosa	19	18			
Invasion adjacent structures	2	2			

reconsidered, however, and additional studies have been conducted. These studies, however, used mainly an intravenous route for drug administration. Studies of adjuvant chemotherapy using long-term oral anticancer drug administration have not been done often in Western countries. We showed the effectiveness of adjuvant chemotherapy in our prior studies using intermittent intravenous administration of 2–4 mg/50 Kg of MMC 8 times in the first weeks following curative resection for colorectal cancer, followed by prolonged oral HCFU treatment at 400 mg/day for 1 year [3]. Based on the positive results of our prior study, a new study designed to examine the effectiveness of long-term oral administration of HCFU alone as adjuvant chemotherapy for colorectal cancer appeared promising. The results of a phase II study involving 30 patients conducted by Koyama [2] showed 43% efficacy (complete response, 1 case; partial response, 12 cases), with few side effects and no alopecia, leukope-

TABLE IV. Carmofur (HCFU) Doses for Patients With Colorectal Cancer: Standard Dosage: 146.0 g

HCFU doses: arm B		
Duration of administration (days)	Cases	
	n	%
30	2	3
31–91	1	1
92–181	4	5
182–291	4	5
292–365	36	47
366–438	28	36
439	2	3

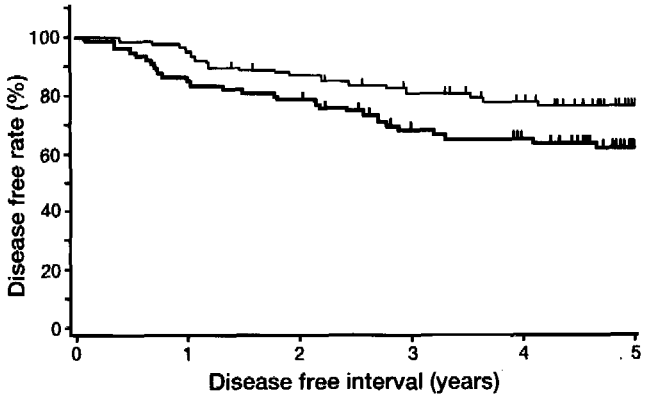

Fig. 1. Disease-free survival rate for all entered patients with colorectal cancer (n = 173). ▬, arm A (control): = 85, 5-year disease-free survival rate 63%; ——, arm B (HCFU): n = 88, 5-year disease-free survival rate 77%. Log-rank test, $P = 0.0407$; generalized Wilcoxon test, $P = 0.0348$.

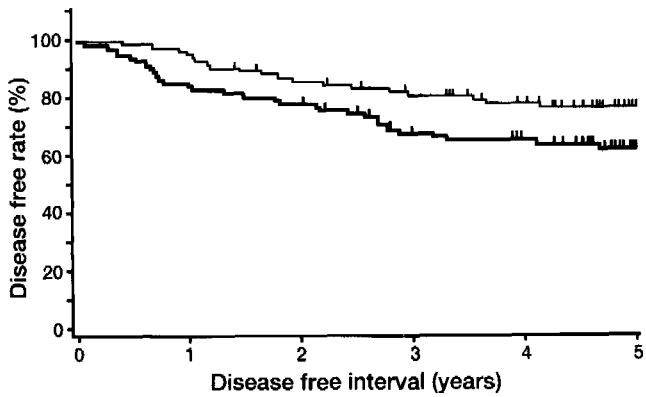

Fig. 2. Disease-free survival rate of evaluable cases of colorectal cancer (n = 159). ▬, arm A: n = 82, 5-year disease-free survival rate 63%; ——, arm B: n = 77, 5-year disease free survival rate 77%. Log-rank test, $P = 0.0469$; generalized Wilcoxon test, $P = 0.0401$.

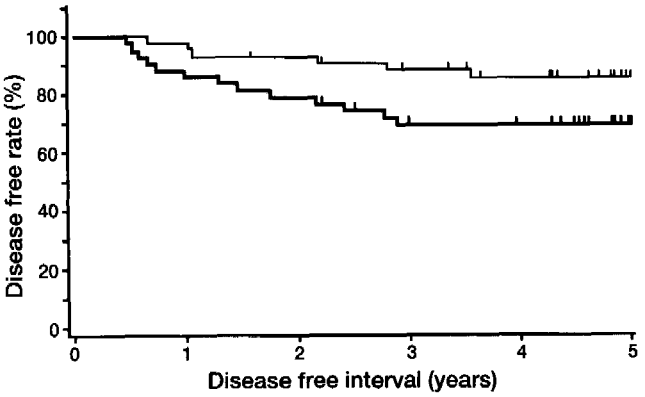

Fig. 3. Disease-free survival rate of evaluable cases of colon cancer (n= 87). ▬, arm A: n = 43, 5-year disease-free survival rate 69%; ——, arm B: n = 44, 5-year disease-free survival rate 86%. Log-rank test, $P = 0.0498$; generalized Wilcoxon test, $P = 0.0436$.

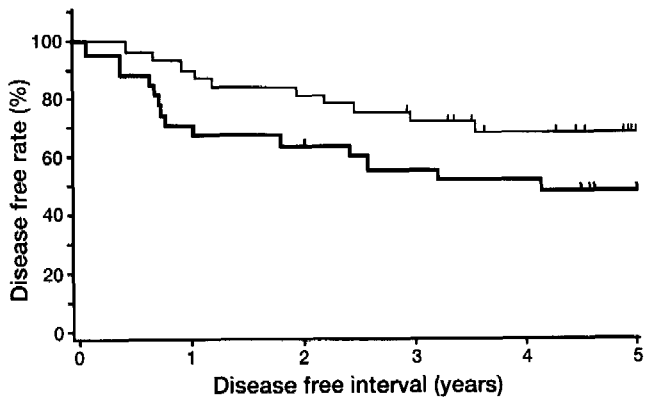

Fig. 4. Disease-free survival rate of evaluable cases with lymph node metastasis of colorectal cancer (n = 62). ▬, arm A: n = 28, 5-year disease-free survival rate 49%; ——, arm B: n = 34, 5-year disease-free survival rate 70%. Log-rank test, $P = 0.0710$; generalized Wilcoxon test, $P = 0.0533$.

TABLE V. Side Effects of Carmofur (HCFU) in Patients With Colorectal Cancer*

HCFU arm B		
	Cases	
	n	%
Frequent urination	8	10
Hot sensation	3	4
Dizziness	3	4
Numbness	2	2
Diarrhea	2	2
Anorexia	1	1
Micturition disorder	1	1
Tinnitus	1	1
Stomatitis	1	1
Irritability	1	1
Nausea or vomiting	1	1

*Entered cases, 88; cases without toxicity, 70 (80%); cases with toxicity, 18 (20%).

nia, or hand-foot syndrome. Thus, HCFU was considered the best anticancer drug in the 5-FU-treated group. The results of the studies by Morioka et al. [9] and Niimoto et al. [10] showed the same effectiveness as in our prior study [4] of patients with colorectal cancer. Because the side effects of HCFU are minimal, there is no need for weekly complete blood cell count tests, and the patient can be followed in the outpatient clinic. This is quite convenient, not only for the physician, but also for the patient, and there is no need to undergo painful phlebotomy for injection. The treatment is also convenient from an economic point of view.

The survival rates of patients with colon cancer classified by tumor location, in arm B (HCFU group) were significantly higher than in arm A (control group), while there was no significant difference between the two arms for patients with rectal cancer. This finding is the same as in the prior studies [3,4], using MMC and HCFU. Recurrences in patients with colon cancer were liver metastasis in 12 patients in arm A and three in arm B (HCFU group), and lung metastasis in three patients in arm A and 2 in arm B. Among the three cases of lung metastasis in arm A, two patients with colon cancer had concomitant liver metastasis. Other distant metastases included one to the abdominal wall and one to the ovaries in arm A patients with colon cancer. One arm B patient with colon cancer had lymph node recurrence. Recurrences among patients with rectal cancer included liver metastasis in 6 patients in arm A and 3 in arm B; lung metastasis in two patients in arm A and 7 in arm B; and distant lymph node metastasis in one patient in arm A and one in arm B. Local recurrences occurred in nine arm A patients and four arm B patients. Among arm B rectal cancer patients were one case of brain metastasis and one of abdominal wall metastasis. It is thought that with colon cancer, the prolongation of life is a result of the prevention of recurrence caused by hematogenous metastasis. In patients with rectal cancer, HCFU had no preventive effect on hematogenous metastasis. The reason for this difference between colon cancer and rectal cancer should be examined in the future.

Side effects due to HCFU occurred in 20% of patients. No cumulative toxicity due to long-term HCFU administration was seen.

CONCLUSION

A randomized controlled study was conducted at seven clinical centers in the Tokai district to confirm the efficacy of HCFU as postoperative adjuvant chemotherapy in patients with colorectal cancer undergoing curative resection.

The results were as follows. Adjuvant chemotherapy with HCFU produced a significant increase in the 5-year disease-free survival rate of patients with colorectal cancer who had a curative resection (log-rank test: $P = 0.0469$, g-Wilcoxon test: $P = 0.0401$). Side effects due to HCFU appeared in 18 of 88 patients (20%) and included pollakisuria, hot sensation, dizziness, numbness, and diarrhea. There were no severe side effects. There was no hand-foot syndrome or alopecia.

From the above results, oral long-term administration of HCFU appears to provide useful and safe postoperative adjuvant chemotherapy for patients with colorectal cancer who have undergone a curative operation.

ACKNOWLEDGMENTS

We thank Mr. Nobuo Ishida for advice concerning the mathematical and statistical analysis of the data and also Miss Masami Sekiya for preparation of the manuscript.

REFERENCES

1. Hoshi A, Iigo M, Kuretani K, et al.: Anti tumor activity of 1-hexylcarbamoyl-5-fluorouracil in a variety of experimental tumors. Gann 67:725–731, 1976.
2. Koyama Y: 1-Hexylcarbamoyl-5-fluorinated pyrimidine. Cancer Treat Rev 8:147–156, 1981.
3. Ito K, Yamaguchi A, Miura K, et al.: Prospective adjuvant therapy with mitomycin C and carmofur (HCFU) for colorectal cancer: ten years follow up. J Surg Oncol 62:4–9, 1996.
4. Ichihashi H, Takagi H, Kondo T, et al.: Prospective adjuvant chemotherapy of mitomycin C plus HCFU for colorectal cancer. 2nd report. 6-year- survival after surgery. Jpn J Cancer Clin 34:451–456, 1988.
5. Higgins GA, Dwight RW, Keehn RJ: Fluorouracil as an adjuvant to surgery in carcinoma of the colon. Ann Surg 173:26–39, 1971.
6. Taylor I, Machin D, Mullee M, et al.: A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. Br J Surg 72:359–363, 1985.
7. Metzger U, Mermillod B, Aeberhard P, et al.: Intraportal chemotherapy in colorectal carcinoma as an adjuvant modality. World J Surg 11:452–458, 1987.
8. Moertel CG, Fleming TR, MacDonald JS, et al.: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 322:352–358, 1990.
9. Morioka K, Muto T, Tomiyama J, et al.: Outcome of adjuvant Mifurolo chemotherapy in patients given a resection of a colonic carcinoma. Jpn J Cancer Clinic 35:1031–1041, 1989.
10. Niimoto M, Hattori T, Inokuchi E, et al.: Mitomycin C plus carmofur (HCFU) adjuvant chemotherapy for noncuratively resected cases of colorectal carcinoma. Interim Report. Jpn J Surg 17:354–361, 1987.